ZONAGEN
INNOVATIVE PRODUCTS FOR
REPRODUCTIVE HEALTH

July 17, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Comments on Docket No. 00D-1278, Federal Register Vol. 65, No. 98, May 19, 2000, entitled: "Draft Guidance for Industry on Female Sexual Dysfunction: Clinical Development of Drug Products for Treatment"

Dear Madam/Sir:

Our company is currently active in the research and development of products for the treatment of Female Sexual Dysfunction (FSD). Therefore, we read your May, 2000 Draft Guidance Document with great interest. Based on these readings we would like to make the following comments for your consideration:

1. Please clarify this guidance by harmonizing the Agency's FSD definition and use of the phrase 'subtype' (Section II) with that of the recent International Consensus Development Conference Report on FSD (Basson R *et al Journal of Urology;* Vol. 163: 888-893, March 2000, enclosed). Note that additional work to be published later this year by experts in the field of FSD is intended to further outline appropriate diagnostic criteria.

2. We assume it is the FDA's intent to minimize recall bias by adding the requirement of daily diaries.

   We question the usefulness of the additional information collected on daily diaries, and fear that they may unnecessarily increase the burden on study participants. Would the FDA provide a further description of what is expected, i.e. the type of information, to be collected on the daily diaries versus the sexual experience [event] diaries?

   Would the FDA please expand and clarify, throughout Sections IV and VI, which type of diary is intended for use in each reference, and the preferred scope of each? Specifically, please clarify the intent (and underlying reasoning) relating to how extensive the daily diary information should be since the event diary information cannot be used for primary endpoint purposes.

00D-1278 C14

2408 Timberloch Place, B-4 ▼ The Woodlands, Texas 77380 ▼ 281-367-5892 ▼ 281-363-8796 Fax

3. Various studies use treatment free diary run-in periods while other studies use placebo run-in periods with diaries.

   For this guidance, does the "pre-treatment" baseline period include or exclude the use of placebo run-in periods, as opposed to treatment free run-in periods? Does pre-treatment mean "pre-randomization" when referring to a study with randomization occurring after a 4 (or 8) week run-in baseline period? Does the FDA have any comments or preferences on the use of either type of baseline evaluation?

4. Two adequate and well-controlled trials of 6 months duration are required for approval (Section IV). Is this study duration supported by published and/or otherwise available data? If so, may the FDA list such references at the end of the document? Perhaps the FDA would specify that this requirement does not pertain to Phase II dose-range finding studies and studies conducted to determine the lowest effective dose.

5. Would the FDA please elaborate on what would be considered a 'clinically significant improvement in event end-points' (section IV) for determination of effectiveness? Would this consideration be based solely on the data provided by the Sponsor as part of its drug development program?

6. Would the FDA please define the term 'linked' as applied to physiological endpoints (Section VI, "physical genital changes"): 'correlated', or 'collected'? Also, please clarify if physiological responses must be linked to a change in the number of successful and satisfying events, if collected, or if this is required only when claiming a surrogate endpoint. Similar questions apply to HRQL claims.

7. Please clarify if successful treatment must distinguish between FSD and normal women for FDSD overall as well as within subtype (or just for indication/subtype sought).

8. How does the FDA classify peri-menopausal women? Would the FDA consider adding this women or patients as a separate subgroup population?

9. Perhaps the FDA could provide its thoughts regarding the concomitant use of lubricants in FSD studies. Although the use of such products could confound the intended treatment effects, not allowing lubricants could jeopardize subject enrollment and study continuation in placebo-controlled studies.

We appreciate the timeliness of this instructive guidance document, and the opportunity to comment. We would welcome an opportunity to discuss this further with Dr. Allen and DRUDP.

Also, we are looking forward to working with the Agency and developing new meaningful therapies for women suffering from FSD.

Sincerely,

Paul Lammers, M.D., M.Sc.
Senior Vice President
Clinical and Regulatory Affairs

Enclosure (1)

cc: Susan Allen, M.D., M.P.H.
Director, Division of Reproductive and Urologic Drug Products (HFD-580)

0022-5347/00/1633-0888/0
THE JOURNAL OF UROLOGY®
Copyright © 2000 by AMERICAN UROLOGICAL ASSOCIATION, INC.®
Vol. 163, 888–893, March 2000
Printed in U.S.A.

REPORT OF THE INTERNATIONAL CONSENSUS DEVELOPMENT CONFERENCE ON FEMALE SEXUAL DYSFUNCTION: DEFINITIONS AND CLASSIFICATIONS

ROSEMARY BASSON,* JENNIFER BERMAN,* ARTHUR BURNETT,* LEONARD DEROGATIS,* DAVID FERGUSON,* JEAN FOURCROY, IRWIN GOLDSTEIN,* ALESSANDRA GRAZIOTTIN,* JULIA HEIMAN,* ELLEN LAAN,* SANDRA LEIBLUM,* HARIN PADMA-NATHAN,* RAYMOND ROSEN,* KATHLEEN SEGRAVES,* R. TAYLOR SEGRAVES,* RIDWAN SHABSIGH,* MARCALEE SIPSKI,* GORM WAGNER* AND BEVERLY WHIPPLE*

ABSTRACT

Purpose: Female sexual dysfunction is highly prevalent but not well defined or understood. We evaluated and revised existing definitions and classifications of female sexual dysfunction.

Materials and Methods: An interdisciplinary consensus conference panel consisting of 19 experts in female sexual dysfunction selected from 5 countries was convened by the Sexual Function Health Council of the American Foundation for Urologic Disease. A modified Delphi method was used to develop consensus definitions and classifications, and build on the existing framework of the International Classification of Diseases-10 and *DSM-IV: Diagnostic and Statistical Manual of Mental Disorders* of the American Psychiatric Association, which were limited to consideration of psychiatric disorders.

Results: Classifications were expanded to include psychogenic and organic causes of desire, arousal, orgasm and sexual pain disorders. An essential element of the new diagnostic system is the "personal distress" criterion. In particular, new definitions of sexual arousal and hypoactive sexual desire disorders were developed, and a new category of noncoital sexual pain disorder was added. In addition, a new subtyping system for clinical diagnosis was devised. Guidelines for clinical end points and outcomes were proposed, and important research goals and priorities were identified.

Conclusions: We recommend use of the new female sexual dysfunction diagnostic and classification system based on physiological as well as psychological pathophysiologies, and a personal distress criterion for most diagnostic categories.

KEY WORDS: sexual dysfunctions, psychological; female; guidelines; classification; Delphi technique

Female sexual dysfunction is a multicausal and multidimensional problem combining biological, psychological and interpersonal determinants. It is age related, progressive and highly prevalent, affecting 20% to 50% of women. Based on epidemiological data from the National Health and Social Life Survey a third of women lack sexual interest and nearly a fourth do not experience orgasm.[1] Approximately 20% of women report lubrication difficulties and 20% find sex not pleasurable. Female sexual dysfunction has a major impact on quality of life and interpersonal relationships. For many women it has been physically disconcerting, emotionally distressing and socially disruptive.

In contrast to the widespread interest in research and treatment of male sexual dysfunction, less attention has been paid to the sexual problems of women. Few studies have investigated the psychological and physiological underpinnings of female sexual dysfunction and fewer treatments are available for women than for men. A major barrier to the development of clinical research and practice has been the absence of a well defined, broadly accepted diagnostic framework and classification for female sexual dysfunction.

Nosological and diagnostic classifications have varied among different diagnostic systems.[2,3] According to the World Health Organization International Classifications of Diseases-10 (ICD-10) the definition of sexual dysfunction includes "the various ways in which an individual is unable to participate in a sexual relationship as he or she would wish."[4] Specific categories in the nomenclature include a lack or loss of sexual desire (F52.0), sexual aversion disorder (F52.1), failure of genital response (F52.2), orgasmic dysfunction (F52.3), nonorganic vaginismus (F52.5), nonorganic dyspareunia (F52.6) and excessive sexual drive (F52.7).

In contrast, the *DSM-IV: Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) of the American Psychiatric Association, which is specifically limited to psychiatric disorders, concerns nomenclature for mental disorders and was not intended to be used for classification of organic causes of female sexual dysfunction.[5] In the DSM-IV sexual dysfunctions are defined as "disturbances in sexual desire and in the psychophysiological changes that characterize the sexual response cycle and cause marked distress and interpersonal difficulty." Disorders in women include hypoactive sexual desire (302.71), sexual aversion (302.79), female arousal disorder (302.72), female orgasmic disorder (302.73), dyspareunia (302.76) and vaginismus (306.51). The DSM-IV provides outcome criteria of "causes marked distress" and "interpersonal difficulty" compared to the broader ICD-10

Accepted for publication October 1, 1999.
Supported by the Sexual Function Health Council of the American Foundation for Urologic Disease through educational grants provided by Affiliated Research Centers, Eli Lilly/ICOS Pharmaceuticals, Pentech Pharmaceuticals, Pfizer Inc., Procter & Gamble, Schering-Plough, Solway Pharmaceuticals, TAP Pharmaceuticals and Zonagen.

* Financial interest and/or other relationship with Affiliated Research Centers, Astra, Bayer AG, Bristol-Myers Squibb, Eli Lilly, Fournier Group, Glaxo Wellcome, Lilly/ICOS, Matrix Pharma, NexMed, NitroMed, Pentech, Pfizer Inc., Pfizer Canada Ltd., Pfizer UK, Pharmacia & Upjohn, Proctor & Gamble, Schering-Plough, Senetek, Shwarz-Pharma, Solvay Pharmaceuticals, Syntec, Syntex, TAP Pharmaceuticals, Vivus and/or Zonagen.

outcome criterion of "being unable to participate in a sexual relationship as he or she would wish." In different ways both systems recognize the need for a subjective distress criterion in defining sexual dysfunction.

The ICD-10 and DSM-IV rely heavily on the human sexual response cycle model first described by Masters and Johnson,[6,7] and later elaborated on by Kaplan.[8,9] This model emphasizes that sexual response involves a temporal sequencing and coordination of several phases, including sexual desire (libido), arousal (excitement), orgasm and satisfaction. Furthermore, both systems are based on the conceptualization of sexual response as a "psychosomatic process" involving psychological and somatic components (ICD-10). The DSM-IV provides a separate diagnostic category of "sexual dysfunction due to a general medical condition" for sexual problems diagnosed as exclusively due to the physiological effects of a medical condition. On the other hand, sexual disorders, such as erectile dysfunction, dyspareunia and vaginismus, are typically diagnosed independently of etiology, which may be largely or entirely organic in some cases. Furthermore, a high degree of overlap or comorbidity has been noted among the sexual disorders, particularly in recent prevalence studies of female dysfunction.[1,10,11] A diagnostic system that is applicable in medical and mental health settings is needed. It may be useful to develop a classification system for female dysfunction that would parallel the clinical and basic science developments for men.[12,13]

The 1992 National Institutes of Health Consensus Development Conference on Impotence set the research agenda for men with a preponderant discussion of organic causes and physical determinants for erectile dysfunction.[12] The major findings included a new definition of erectile dysfunction, comprehensive review of etiology and pathophysiology, and guidelines for clinical diagnosis. The consensus statement had immediate and far reaching effects in shaping the direction of research in basic and industry related studies of male sexual dysfunction. Since the approval of sildenafil a more recent consensus panel has recommended use of a process of care model for patient assessment and treatment, including an emphasis on educational interventions and a step care treatment algorithm.[13]

Research on the causes and treatment of female sexual dysfunction has lagged far behind. Recently an international multidisciplinary consensus development conference on female sexual dysfunction was convened to begin to address the shortcomings and problems associated with previous classifications of female sexual dysfunction. We reviewed and evaluated scientific information as well as current research and clinical practice in the field. The resulting guidelines were intended to be used by health care professionals and the general public. A specific goal was to develop a consensus based definition and classification system for female sexual dysfunction that would include psychogenic and organically based disorders. Other objectives were to develop guidelines for clinical evaluation and end points, and identify critical knowledge gaps and priorities for future research. We describe the results of the first International Consensus Development Conference on Female Sexual Dysfunction.

METHODS

The first Consensus Development Panel on Female Sexual Dysfunction was convened by the Sexual Function Health Council of the American Foundation for Urologic Disease. An initial planning meeting was held in conjunction with the biannual meeting of the International Society of Impotence Research in Amsterdam in August 1998. The overall aim was to identify a multidisciplinary group of experts in the field of female sexuality, and develop a conference format and agenda. Panel co-chairs were selected, and the format and composition of the consensus panel were established.

All panelists were selected on the basis of research or clinical expertise in female sexual dysfunction as well as their position as "thought leaders" in this emerging field. Nominations were provided by specialty societies, and authorship of key publications was considered. The final panel comprised leading European and North American investigators with representation from academic and private practice settings. The 19 panelists from Canada, Denmark, Italy, The Netherlands and the United States represented a wide range of disciplinary backgrounds, including endocrinology, family medicine, gynecology, nursing, pharmacology, physiology, psychiatry, psychology, rehabilitation medicine and urology. Each panelist fulfilled the aforementioned criteria and is currently involved in research or treatment of female sexual disorders. Full attendance at the consensus conference meeting was required.

The consensus panel meeting on October 22, 1998 in Boston consisted of closed session deliberations and involved several key decision making components. Before the conference all panelists were provided with a complete bibliography and readings on female sexual dysfunction, particularly concerning physiology, pathophysiology, definition, classification, epidemiology, diagnosis and treatment. A meeting agenda and list of objectives were also provided in advance. The meeting began with a review of current epidemiological data on female sexual dysfunction, advantages and disadvantages of the human sexual response cycle model, and strengths and weaknesses of existing diagnostic systems. Subsequently the panel began consensus deliberations involving use of the Rand methodology for development of new definitions and a classification system for female sexual dysfunction. The meeting duration was more than 15 hours.

Criteria for diagnostic decision making were evaluated with a modified Delphi method. This consensus development method involves intensive review of a specific topic area by an expert panel, structured group discussion and consensus voting according to a strict mathematical formula.[14] The approach is widely referred to as the Rand method for medical decision making and technology assessment.[14,15] It synthesizes the opinions of clinicians and research experts, and is designed to develop consensus guidelines regarding the appropriateness of use of clinical procedures or diagnostic decision making.[15] By drawing on the clinical knowledge and experience of experts the process provides detailed clinical guidelines for a broad range of situations. The advantages are cost-effectiveness and timeliness, as the method draws on a broad base of clinical and research data available at assessment. The principal disadvantages are the limitations of currently available data and the subjective nature of the group decision making process. Fundamental elements include panel selection, development of appropriateness scales and panel preparation, and a modified Delphi technique for decision making and consensus development, group discussion and reevaluation of the resulting consensus guidelines.

Panelists were invited to base judgments on personal views and not the position of the society that may have nominated them. A clinical definition or diagnosis was considered appropriate when there was sufficient consensus, which was based on group ratings on a 9-point scale of clinical appropriateness. Panel consensus voting was used to decide whether a particular definition or diagnosis was appropriate for a homogeneous category of patients. A definition was deemed clearly appropriate if the median rating was 7 to 9 and clearly inappropriate if it was 1 to 3 points. Equivocal definitions were those with ratings in the 4 to 6-point range or when panelists disagreed on the proper rating.

All ratings were confidential. Median rating was used as a measure of the central tendency of panelist ratings. Measures of agreement and disagreement were also tabulated. To obtain definitions that panelists accepted as reasonable the

extreme low and high scores were excluded from the median calculation. Another concept for agreement was that ratings needed to be clustered in any 3-point range, even if the range straddled the appropriateness categories defined previously. If no agreement was reached, further discussion occurred and the vote was retaken. A maximum of 2 votes was permitted on any specific issue. Expert panel review and subcommittee deliberations were held before preparation of the final report.

RESULTS

The final classification system, which follows the same general structure as the DSM-IV and ICD-10, is shown in the Appendix. It is noteworthy that the 4 major categories of dysfunction, that is desire, arousal, orgasmic and sexual pain disorders, described in the DSM-IV and ICD-10 were preserved, which was considered necessary to maintain continuity in research and clinical practice. On the other hand, the definitions of several disorders have been altered to reflect current clinical and research practice, and a new category of sexual pain disorder, including noncoital sexual pain, has been added.

Definitions. Sexual Desire Disorders: Hypoactive sexual desire disorder is the persistent or recurrent deficiency (or absence) of sexual fantasies/thoughts, and/or desire for or receptivity to sexual activity, which causes personal distress. Sexual aversion disorder is the persistent or recurrent phobic aversion to and avoidance of sexual contact with a sexual partner, which causes personal distress.

Sexual Arousal Disorder is the persistent or recurrent inability to attain or maintain sufficient sexual excitement, causing personal distress, which may be expressed as a lack of subjective excitement, or genital (lubrication/swelling) or other somatic responses.

Orgasmic Disorder is the persistent or recurrent difficulty, delay in or absence of attaining orgasm following sufficient sexual stimulation and arousal, which causes personal distress.

Sexual Pain Disorders: Dyspareunia is the recurrent or persistent genital pain associated with sexual intercourse. Vaginismus is the recurrent or persistent involuntary spasm of the musculature of the outer third of the vagina that interferes with vaginal penetration, which causes personal distress. Noncoital sexual pain disorder is recurrent or persistent genital pain induced by noncoital sexual stimulation.

Each of these diagnoses is subtyped as A—lifelong versus acquired type, B—generalized versus situational type and C— etiologic origin (organic, psychogenic, mixed, unknown). Subtyping is based ideally on the best available evidence from the medical history, laboratory tests and physical examination. For example, the diagnosis of vaginismus would be based in part on history of sexual difficulties as well as patient inability to tolerate insertion of a speculum during a pelvic examination. It is noteworthy that some women with vaginismus are able to tolerate speculum insertion.

End points and outcomes. For clinical trials it is necessary to specify clear end points and outcomes for female sexual dysfunction. This task is not simple, given that common sexual problems in women, such as low desire and anorgasmia, frequently involve overlapping subjective and physiological components.[10] Additionally, there appears to be significant co-morbidity among diagnostic categories (for example desire, arousal, orgasm, sexual pain disorders) which is not always classifiable according to a primary or secondary diagnosis. A composite measure of sexual response, if statistically sound, might be a useful overall outcome index.

Clinical trial research in female sexual dysfunction is in the earliest stages. Accordingly, there are no widely used or standardized end points. For future trials end points should be based on the consensus conference definitions. For hypoactive sexual desire disorder clinical end points should include measures of receptivity to as well as spontaneous thoughts or fantasies about sexual activity. For sexual arousal disorder in women clinical end points should include measures of peripheral (lubrication, swelling) and central (subjective arousal) responses to sexual stimulation. Changes in sexual responsiveness should be associated with a measurable decrease in personal distress as well as improvement in overall sexual satisfaction.

Several questionnaire measures of female sexual function are available in the literature and some meet basic psychometric criteria.[16,17] However, the published questionnaires were developed before the current classification and do not address some aspects of current definitions. Specific measures of personal distress are not included in these measures. Other self-report measures described in the literature include structured interviews, event logs and patient diary methods. Global assessments of efficacy are also used in many clinical trials, and are potentially useful as primary or secondary end points, depending on the study design and trial setting. Further standardization and validation of these measures are strongly recommended. New questionnaire and diary measures are in development and hopefully will be available shortly for use in clinical trials. Validation of these instruments should be conducted before or in conjunction with ongoing clinical trials.

To date vaginal photoplethysmography has been the most widely used physiological measure, demonstrating adequate validity and reliability in psychophysiological studies of healthy and sexually dysfunctional women. Major drawbacks include the absence of an absolute standard of measurement, wide individual differences and potential susceptibility to movement artifacts.[18,19] The method is best suited for within subject, repeat measures designs (phase II trials) in which careful control of stimulus conditions and response variables is maintained. Several other physiological measurement approaches have been proposed and are in development, including measures of clitoral and labial temperature and oxygenation, vaginal and clitoral Doppler and blood flow measures, and vaginometry.[20] Despite the obvious interest and appeal of these alternative measures, none has been adequately validated or standardized in patients or healthy controls. Quality of life measures are important in clinical trials of sexual dysfunction, particularly measures of personal distress. To date there are no standardized measures of distress related to sexual dysfunction in women. This area is important for future development.

Research needs and priorities. Female sexual dysfunction is an under researched and poorly understood area. The lack of adequate experimental or clinical trial data was a consistent theme of the panel deliberations. Recognizing the broad need for basic and applied research in the area, the panel identified major themes or topics for further research.

Epidemiological research on the prevalence, predictors and outcomes of sexual dysfunction in women is urgently needed. A recent study indicated that sexual dysfunction is highly prevalent in women but was limited to those younger than 60 years and did not include a detailed clinical evaluation.[1] Further epidemiological studies are needed and should be based on the consensus definitions of sexual dysfunction.

Anatomical studies are needed to delineate more precisely the pathway of vital nerves, arterial inflow and venous drainage of the multiple organs involved in normal female sexual function. This knowledge may not only improve physiological understanding of the sexual response, but also may lead to innovative nerve sparing operative approaches during pelvic surgery.

Biological mechanisms of sexual arousal and orgasm in women are poorly understood at present. For example, the

neurophysiology of the female sexual response, including the role of neurotransmitters and local vasoactive substances in determining vascular smooth muscle tone, vasodilation and vaginal lubrication, has not been adequately studied. Likewise, the role of steroid hormones in the modulation of sexual desire and arousal in women is not well understood.

The effects of aging and menopause on female sexual functioning are important areas for further research. Of the factors mediating the effects of aging on sexual function in women the role of hormones, psychosocial and interpersonal factors, medication use and concomitant illnesses have not been adequately delineated.

The relationship among sexual dysfunction in women, physical or emotional distress and overall quality of life is highly variable. Conversely, many women experience a lack of satisfaction with their sexual relationship, despite the ability to achieve arousal or orgasm. Many studies have noted a lack of association between physiological and subjective concomitants of arousal in women. This phenomenon is only minimally understood at present.[21,22] The determinants of sexual desire in women also remain to be evaluated.

Urgent investigation is needed concerning development of reproducible measurement devices and instruments for evaluating physiological parameters of the female sexual response in the clinical setting. Parameters should include but are not limited to measurements of genital blood flow, genital engorgement, genital sensation, vaginal lubrication and vaginal elasticity.

Clinical trials of vasoactive agents and steroidal therapies are strongly encouraged. It is uncertain whether vasoactive drugs widely used for treatment of male erectile dysfunction will have clinical usefulness in the treatment of specific dysfunctions in women. Likewise, controlled outcome studies of psychosexual counseling for various indications are strongly indicated. The safety and effectiveness of specific treatments in defined patient populations (for example postmenopausal, post-hysterectomy or other pelvic surgery, spinal cord injury, post-cancer therapy) remain to be evaluated. Although there is evidence that psychological sex therapy interventions are efficacious for some disorders, further clinical trials of psychosexual therapy alone or in combination with pharmacological treatment are needed.

Finally, studies of physician awareness and competency in female sexual dysfunction are urgently needed. Most physicians and other health care providers receive little or no formal training in this area. Physician and patient needs are not well defined, nor are the public health or cost implications.

DISCUSSION

Female sexual dysfunction is a highly prevalent condition, affecting up to 40% of women in the United States.[1,11] A strong need has been identified for new definitions and classification of female sexual dysfunction as well as a new set of diagnostic criteria. The consensus conference was convened specifically to meet these needs. While the major categories of sexual dysfunction in the ICD-10 and DSM-IV were preserved, in the absence of evidence based justification for departure from these systems, significant changes were made in several areas.

The definition of hypoactive sexual desire was broadened to include a lack of receptivity to sexual activity. Hypoactive sexual desire is difficult to define in absolute terms given the lack of reliable population norms.[1,10] However, the proposed definition emphasizes the persistent lack or deficiency of well accepted markers of desire, such as sexual thoughts or fantasies and desire for or receptivity to initiation by a partner. The 2 important elements in the new definition are the persistent lack of desire and resulting personal distress. Thus, the definition would not apply to the woman who lacks desire only in some circumstances (for example during periods of marital conflict) or at certain times (for example before or during menstruation). Similarly, even if sexual desire was persistently lower than that of the partner or women of comparable age and socioeconomic status, the definition would not apply in the absence of personal distress related to the problem.

Some panelists questioned the inclusion of sexual aversion in the broader category of sexual desire disorders, although currently there is not enough evidence to warrant removal of the category or placement in a different dimension. It was noted that some patients with this diagnosis have apparent desire for sexual contact but are unable to initiate or respond to contact due to phobic aversion. Further research on this topic and the etiology of sexual desire disorders in general is strongly recommended.

The definition of sexual arousal disorder was expanded to incorporate nongenital and subjective dimensions of arousal. Recognizing the wide range of physical and subjective reactions that characterize female sexual arousal, the new definition refers to "lack of subjective excitement or a lack of genital (lubrication/swelling) or other somatic responses." This new definition is more inclusive than the ICD-10 definition of "failure of genital response."

A new category of noncoital sexual pain disorder was added to the classification system, which is to be applied to recurrent or persistent genital pain induced by noncoital sexual stimulation. It was noted that a significant number of women experience pain during noncoital forms of sexual stimulation who would not be included in the current categories of vaginismus or dyspareunia. This new category is also important in recognizing that sexual activity for women need not necessarily involve penile vaginal intercourse and the category of sexual pain disorder may apply to nonheterosexual women engaging in alternative sexual behaviors.

An essential element of the new diagnostic system is the inclusion of a personal distress criterion for most of the diagnostic categories. Thus, for hypoactive sexual desire disorder, sexual arousal disorder, orgasmic disorder and vaginismus an essential element of the diagnosis is the requirement that the condition causes significant personal distress for the individual. The assessment of personal distress can be made via clinical interview or standardized questionnaire. Existing measures of distress can be used or disease specific assessment instruments could be developed. Currently there are no validated sexual distress specific instruments for immediate use in clinical trials of female sexual dysfunction.

Clinician assessment of personal distress involves querying the patient about the level of dissatisfaction or bother concerning the sexual difficulty. For example, a woman who seldom reaches orgasm may report that it does not bother her particularly and that she is still able to enjoy sexual relations with her partner. Similarly, some women do not view low sexual desire as a personal problem. In these instances a diagnosis of sexual dysfunction would not be given due to the absence of personal distress on the part of the patient. The reaction of the sexual partner may be a cause of concern or bother to the patient but is insufficient as a basis for diagnosis. For instance, if a woman reports that her partner is dissatisfied with her lack of orgasm but that it does not bother her personally, a specific diagnosis would not be given. Counseling may still be recommended in such cases due to the conflict or incompatibility in expectations regarding adequate sexual functioning.

In contrast to the DSM-IV, which was developed to provide nomenclature for mental conditions and, thus, limited to consideration of psychiatric disorders, the new consensus classification system applies to all forms of female sexual dysfunction regardless of etiology. Thus, organic and psycho-

genic forms of sexual dysfunction are included in the present classification. The fact that many dysfunctions in women are not exclusively psychologically or organically based is generally accepted. For example, physical findings of hypersensitivity and allodynia of the vestibular margin in some cases of dyspareunia or increased muscle tone in the perivaginal muscles often associated with vaginismus may be associated with strong central or psychological determinants.[23] A new typology for differentiating organic, psychogenic, mixed and uncertain etiologies is included in the proposed subtyping. The etiological category of "unknown" was added, which is recommended for use when the diagnosing clinician has inadequate basis for etiological formulation, based on patient history, physical examination or laboratory tests.

Finally, there were extended discussions among panelists about the introduction of a new diagnostic category of sexual satisfaction disorder. It was proposed that this diagnosis be applied when a woman is unable to achieve subjective sexual satisfaction, despite adequate desire, arousal and orgasm. It was noted by several panelists that this diagnosis applied to a significant number of women who sought help for sexual dysfunction. Complaints of this type are difficult to incorporate within the existing nosological framework. It was also suggested that publication of a new diagnostic category would stimulate research on the epidemiological prevalence of the disorder as well as studies of the underlying mechanisms and psychological processes. On the negative side of the issue, several panelists noted the absence of adequate epidemiological or clinical evidence in support of this new category. The difficulty in defining diagnostic thresholds or criteria for making the diagnosis was also noted. Although a majority of panelists favored introduction of this new category, following 2 rounds of voting and discussion the panel failed to reach satisfactory consensus. Instead, a recommendation was made to reconsider this proposal when additional epidemiological and clinical data become available. Further research on this topic is strongly encouraged.

Clearer specification of end points and outcomes is required for clinical trials of female sexual dysfunction. We reached several major conclusions. Clinical end points should be based on the consensus guidelines for definition and classification of female sexual dysfunction. For large scale clinical trials patient self-report measures are generally preferred, which could include standardized questionnaires or event log types of measures. Specific changes in sexual function should be defined as primary and secondary end points in all clinical trials. In accordance with the current consensus definitions, measures of personal distress should be included with other quality of life measures, which in most instances will serve as important secondary end points. Physiological end points, such as vaginal photoplethysmography or vaginal ultrasound, are of potential value in investigations of drug dosages or mechanisms of action. When such measures are used, emphasis needs to be placed on the conditions of stimulation and laboratory setting in which the research is conducted. Further research is urgently needed on the sensitivity and reliability of patient based and physiological measures of sexual response in women.

CONCLUSIONS

We considered the previous diagnostic systems proposed by the DSM-IV and ICD-10, used a modified Delphi method for determining the appropriateness of each category and definition, and expanded definitions to include physical as well as psychological causes of female sexual dysfunction. Although the 4 major categories of desire, arousal, orgasmic and sexual pain disorders in the DSM-IV were retained, several changes were made in the specific definitions and criteria for each diagnosis, including use of a personal distress criterion for most diagnostic categories. A new diagnosis of noncoital sexual pain disorder was added to the category of sexual pain disorders and a new diagnostic category of sexual satisfaction disorder was proposed but failed to achieve complete consensus approval. In addition to the consensus classification system, guidelines concerning clinical end points and outcomes in female sexual dysfunction were developed, and a list of current research topics and priorities was proposed.

Thomas Bruckman and Bette Rank, American Foundation for Urologic Disease, provided support and assistance.

APPENDIX: CLASSIFICATION OF FEMALE SEXUAL DYSFUNCTION

1999 Consensus Classification System

I. Sexual desire disorders:
   A. Hypoactive sexual desire disorder
   B. Sexual aversion disorder
II. Sexual arousal disorder
III. Orgasmic disorder
IV. Sexual pain disorders:
   A. Dyspareunia
   B. Vaginismus
   C. Other sexual pain disorders

REFERENCES

1. Laumann, E. O., Paik. A. and Rosen, R. C.: Sexual dysfunction in the United States: prevalence and predictors. JAMA, **10:** 281: 537, 1999
2. Vroege, J. A., Gijs, L. and Hengeveld, M. W.: Classification of sexual dysfunctions: towards DSM-V and ICD-11. Compr Psychiatry, **39:** 333, 1998
3. Leiblum, S. R.: Definition and classification of female sexual disorders. Int J Impot Res, suppl., **10:** S104, 1998
4. World Health Organization: ICD-10: International Statistical Classification of Diseases and Related Health Problems. World Health Organization: Geneva, 1992
5. American Psychiatric Association: DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington. D. C.: American Psychiatric Press, 1994
6. Masters, W. H. and Johnson, V. E.: Human Sexual Response. Boston: Little Brown, 1966
7. Masters, W. H. and Johnson, V. E.: Human Sexual Inadequacy. Boston: Little Brown, 1970
8. Kaplan, H. S.: Disorders of Sexual Desire. New York: Brunner/Mazel, 1979
9. Lief, H. I.: Inhibited sexual desire. Med Aspects Hum Sex, **7:** 94. 1977
10. Segraves, K. B. and Segraves, R. T.: Hypoactive sexual desire disorder: prevalence and comorbidity in 906 subjects. J Sex Marital Ther, **17:** 55, 1991
11. Rosen, R. C., Taylor, J. F., Leiblum, S. R. et al: Prevalence of sexual dysfunction in women: results of a survey study of 329 women in an outpatient gynecological clinic. J Sex Marital Ther, **19:** 171, 1993
12. National Institutes of Health Consensus Development Panel on Impotence: Impotence. JAMA, **270:** 83, 1993
13. The Process of Care Consensus Panel: The process of care model for evaluation and treatment of erectile dysfunction. Int J Impot Res, **11:** 59, 1999
14. Kahn, K. L., Kosecoff, J., Chassin, M. R. et al.: Measuring the clinical appropriateness of the use of a procedure. Can we do it? Med Care, **26:** 415, 1988
15. Brook, R. H., Chassin, M. R., Fink, A. et al.: A method for the detailed assessment of the appropriateness of medical technologies. Int J Technol Assess Health Care, **2:** 53, 1986
16. Derogatis, L. R. and Melisaratos, N.: The DSFI: a multidimensional measure of sexual functioning. J Sex Marital Ther. **5:** 244, 1979
17. Taylor, J. F., Rosen, R. C. and Leiblum, S. R.: Self-report assessment of female sexual function: psychometric evaluation of the Brief Index of Sexual Function for Women. Arch Sex Behav. **23:** 627, 1994

18. Laan, E. and Everaerd, W.: Physiological measures of vaginal vasocongestion. Int J Impot Res, suppl., **10:** S107, 1998
19. Rosen, R. C. and Beck, J. G.: Patterns of Sexual Arousal: Psychophysiological Processes and Clinical Applications. New York: Guilford Press, 1988
20. Goldstein, I. and Berman, J. R.: Vasculogenic female sexual dysfunction: vaginal engorgement and clitoral erectile insufficiency syndromes. Int J Impot Res, suppl., **10:** S84, 1998
21. Laan, E., Everaerd, W., van der Velde, J. et al: Determinants of subjective experience of sexual arousal in women: feedback from genital arousal and erotic stimulus content. Psychophysiology, **32:** 444, 1995
22. Heiman, J. R.: Psychophysiological models of female sexual response. Int J Impot Res, suppl., **10:** S94, 1998
23. Basson, R.: The female sex response: a different model. J Sex Marital Ther, in press

FedEx USA Airbill

FedEx Tracking Number: 8204 2427 2886

Form I.D. No. 0215

2DA21

Recipient's Copy

RECIPIENT: PEEL HERE

1 From This portion can be removed for Recipient's records.

Date 7/19/00 FedEx Tracking Number 820424272886

Sender's Name Paul Simmons Phone 281 367-5892

Company ZONAGEN INC

Address 2408 TIMBERLOCH PL STE B4 Dept/Floor/Suite/Room

City THE WOODLANDS State TX ZIP 77380

2 Your Internal Billing Reference Comments

3 To

Recipient's Name Dockets Mgmt Branch Phone

Company Food + Drug Administration

Address 5630 Fishers Ln. Rm 1061

To "HOLD" at FedEx location, print FedEx address. We cannot deliver to P.O. boxes or P.O. ZIP codes.

City Rockville State MD ZIP 20852 Dept/Floor/Suite/Room

8204 2427 2886

0141538385

4a Express Package Service — *Packages up to 150 lbs.* Delivery commitment may be later in some areas.

- [x] FedEx Priority Overnight — Next business morning
- [ ] FedEx Standard Overnight — Next business afternoon
- [ ] FedEx First Overnight — Earliest next business morning delivery to select locations
- [ ] FedEx 2Day* — Second business day
- [ ] FedEx Express Saver* — Third business day

* FedEx Envelope/Letter Rate not available. Minimum charge: One-pound rate

4b Express Freight Service — *Packages over 150 lbs.* Delivery commitment may be later in some areas.

- [ ] FedEx 1Day Freight* — Next business day
- [ ] FedEx 2Day Freight — Second business day
- [ ] FedEx 3Day Freight — Third business day

* Call for Confirmation: _____

5 Packaging — * Declared value limit $500

- [x] FedEx Envelope/Letter*
- [ ] FedEx Pak*
- [ ] Other Pkg. Includes FedEx Box, FedEx Tube, and customer pkg.

6 Special Handling — Include FedEx address in Section 3.

- [ ] SATURDAY Delivery — Available for FedEx Priority Overnight and FedEx 2Day to select ZIP codes
- [ ] SUNDAY Delivery — Available for FedEx Priority Overnight to select ZIP codes
- [ ] HOLD Weekday at FedEx Location — Not available with FedEx First Overnight
- [ ] HOLD Saturday at FedEx Location — Available for FedEx Priority Overnight and FedEx 2Day to select locations

Does this shipment contain dangerous goods? One box must be checked.

- [x] No
- [ ] Yes — As per attached Shipper's Declaration
- [ ] Yes — Shipper's Declaration not required
- [ ] Dry Ice — Dry Ice, 9, UN 1845 ____ x ____ kg

Dangerous Goods cannot be shipped in FedEx packaging.

- [ ] Cargo Aircraft Only

7 Payment *Bill to:* Enter FedEx Acct. No. or Credit Card No. below.

- [x] Sender — Acct. No. in Section 1 will be billed.
- [ ] Recipient
- [ ] Third Party
- [ ] Credit Card
- [ ] Cash/Check
- [ ] Obtain Recip. Acct. No.

FedEx Acct. No. [redacted]

Total Packages	Total Weight	FedEx Use	Total Charges
1		[redacted]	Credit Card Auth.

†Our liability is limited to $100 unless you declare a higher value. See the *FedEx Service Guide* for details.

8 Release Signature *Sign to authorize delivery without obtaining signature.*

By signing you authorize us to deliver this shipment without obtaining a signature and agree to indemnify and hold us harmless from any resulting claims.

Questions? Call 1·800·Go·FedEx® (800-463-3339)

Visit our Web site at www.fedex.com

359